TXR NO. 0050473

February 14, 2002

MEMORANDUM

SUBJECT: ***ENDOSULFAN*** - Report of the FQPA Safety Factor Committee.

NOTE: THIS REPORT REPLACES THE PREVIOUS REPORT OF THE FQPA SAFETY FACTOR COMMITTEE DATED NOVEMBER 20, 1998 (HED DOC. NO. 012974).

FROM: Carol Christensen, Acting Executive Secretary
FQPA Safety Factor Committee
Health Effects Division (7509C)

THROUGH: Ed Zager, Chair
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PC Code: 079401

The Health Effects Division (HED) FQPA Safety Factor Committee met on February 11, 2002 to re-evaluate the hazard and exposure data for endosulfan and recommended that the FQPA Safety Factor (as required by Food Quality Protection Act of August 3, 1996) be retained **(10x)** in assessing the risks posed by this chemical.

I. HAZARD ASSESSMENT

(Correspondence: D. Locke and E. Mendez to C. Christensen February 7, 2002)

1. Adequacy of the Toxicity Database

The endosulfan database contains acceptable guideline studies to evaluate the effects of endosulfan exposure both *in utero* and in young animals. The HIARC determined that the requirement for a developmental neurotoxicity study in rats was reserved for endosulfan pending the receipt and review of a subchronic neurotoxicity studies in rats. However, **the FQPA Safety Factor Committee concluded that a developmental neurotoxicity study in rats is required for endosulfan** due to concern by the Committee for: 1) the fetal effects reported in the open literature abstract; 2) the severity of effects seen in the female offspring of the F_0 generation (increased pituitary weight) and F_1b generation (increased uterine weights) at the high-dose when compared to the toxicity observed in parental animals (decreased body weight) at this dose in the two-generation reproduction study in rats; and 3) the subchronic neurotoxicity study (requested by the HIARC) will only address the neuropathological concerns resulting from exposure to endosulfan - a developmental neurotoxicity study will provide the critical data demonstrating the toxic effects of endosulfan on the developing fetal nervous system.

2. Determination of Susceptibility

A. The Hazard Identification Assessment Review Committee (HIARC) determined that under the conditions of the available Agency Guideline studies, there is no evidence of enhanced susceptibility of the offspring to exposure to endosulfan. In the prenatal developmental toxicity studies in rats and rabbits, developmental toxicity was seen only in the presence of maternal toxicity. Furthermore, the severity of developmental effects seen in these studies is comparable to the severity of effects seen in adult animals. In the two-generation reproduction study in rats, effects in the offspring were observed only at or above treatment levels which resulted in evidence of parental toxicity (*Memorandum:* D. Liem and J. Rowland to S. DeVito dated October 7, 1998).

B. A recent review by the Agency for Toxic Substances and Disease Registry (ATSDR) reported the results of non-guideline studies which demonstrated that young rats may be more susceptible than older rats upon exposure to endosulfan. Studies conducted by Zaidi *et al.* (1985) and Sinha *et al.* (1995 & 1997) illustrate effects to the offspring at doses lower than those showing effects in adults. In the first, neonatal rat pups were dosed for 25 days intraperitoneally and displayed increased serotonin binding to the frontal cortical membranes of the brain and increased aggressive behavior. Adults exposed in a similar manner did not display these effects. In a study by Sinha *et al.*, both three week and three months old rats were treated orally; decreased intratesticular spermatid count and increased percentage of abnormal sperm were seen in three week old rats at doses lower than those eliciting similar effects in three month old rats.

4. Evidence for Endocrine Disruption

A. There is evidence for endocrine disruption both in studies submitted to the Agency and those published in the open literature. In the chronic toxicity/carcinogenicity study in rats, endosulfan induced testicular atrophy and parathyroid hyperplasia. In the multi-generation reproduction study, increased pituitary and uterine weights were seen. Endosulfan is considered to be an endocrine disruptor. Substances that act as endocrine disruptors may perturb the endocrine system in a variety of ways including but not limited to interfering with the synthesis, secretion, or transport of hormones in the organism. The Agency emphasizes the fact that the endocrine system integrates a variety of CNS-pituitary-target organ pathways that not only affect reproductive or sexually regulated parameters but also regulates a wide array of bodily functions and homeostasis.

B. The ATSDR, 2000 reported a number of studies that assessed endosulfan's effects on the endocrine system. Singh and Pandey (1989) dosed adult rats orally for 7 days and observed decreased testicular testosterone in conjunction with increased serum testosterone which suggests sec-hormone binding globulin (SHBG) may be affected. In a subsequent study, these researchers dosed rats orally for 15-30 days. Under the conditions of this study, decreases in testicular testosterone, plasma testosterone, LH, and FSH as well as decreased steroidogenic enzyme and cytochrome P-450-dependent monooxygenase were reported. These decreases in LH may lead to decreases in the activity of Steroidogenic Acute Regulatory Protein (responsible for translocation of cholesterol to the inner mitochondria) and may therefore affect the conversion of cholesterol to testosterone. Vonier *et al.* (1996) conducted a competitive binding assay using alligator oviduct tissue and found endosulfan exposure significantly inhibited ^{3}H-17-estradiol binding to the estrogen receptor and progestin ^{3}H-R5020 binding to the progesterone receptor. Ramamoorthy *et al.* used the yeast reporter system to discover endosulfan induced human-ER-mediated-gal activation. Endosulfan induced galactosidase transcription/expression to about 32% of the induction seen after estradiol treatment at 0.01 µM. In a study conducted by Sinha *et al.* (1995) rats dosed orally with endosulfan for 70 days exhibited decreases in sperm counts in the cauda epididymis as well as decreased intratesticular spermatid counts. Finally, Lakshmana *et al.* (1994) showed endosulfan induces small but significant changes in the levels of noradrenaline, dopamine and serotonin in the developing rat brain and deficits in the operant learning performance suggesting possible effects on the neuroendocrine system.

II. EXPOSURE ASSESSMENT AND RISK CHARACTERIZATION

(*Note: The only change to the exposure assessment and risk characterization since the 20 November 1998 FQPA SFC Meeting is the cancellation of the residential uses for endosulfan.)*

1. Dietary (Food) Exposure Considerations

Endosulfan is widely used on many agricultural crops and also in residential settings as an insecticide and acaricide. The chemical is a mixture of isomers and the tolerance expression includes the alpha, beta isomers plus a sulfate metabolite.

Tolerances for residues of endosulfan and its metabolites are established in/on many RACs including fruits, vegetables grains, milk and meat at levels ranging from 0.1 ppm to 2.0 ppm (40CFR180.182). Codex maximum residue limits (MRLs) for residues of endosulfan are established in/on various plant and animal commodities.

There are numerous field trial data on various commodities, reflecting various application sites throughout the country. Additionally, PDP and FDA monitoring data are available for endosulfan. Residues of endosulfan have been reported by PDP and FDA in a variety of crops. For example, in 1995 endosulfan was detected in apples (7%), carrots (4%), grapes (4%), green beans (24%), peaches (8%), potatoes (20%), spinach (14%), corn (0.1%), peas (0.3%), and oranges (2%) - for which there is no tolerance. The Limit of Quantitation (LOQ) for these data is ~0.01 ppm.

The HED Dietary Exposure Evaluation Model (DEEM) is used to assess the risk from acute and chronic dietary exposure to residues of endosulfan in food. These analyses are based on the consumption database used by DEEM and residue information from monitoring studies.

2. Dietary (Drinking Water) Exposure Considerations

The environmental fate data base for endosulfan is adequate for risk assessment. Endosulfan may be moderately persistent in soils but its high affinity to sorb to soil particles, reduces its susceptibility to leaching. Although endosulfan does not appear to be highly mobile, it may be persistent enough in some instances to move to ground water (detects have been reported in the EPA Pesticides in Ground Water Database). Movement to surface water sources of drinking water is likely to occur via spray drift and runoff adsorbed to soil particles. This is supported by several studies which have reported endosulfan detects in surface water.

Endosulfan consists of isomers which appear to have some differences in persistence. Endosulfan sulfate and its isomers are the degradates of concern. Ground water and surface water EECs for endosulfan will be based upon modeling and supported by any available monitoring data. The EFED models are used for ground and surface source drinking water exposure assessments.

3. Residential Exposure Considerations

Uses of endosulfan in the residential environment have been canceled.

III. SAFETY FACTOR RECOMMENDATION AND RATIONALE

1. FQPA Safety Factor Recommendation

The Committee recommended that the **FQPA safety factor** for protection of infants and children (as required by FQPA) be **retained (10x).**

2. Rationale for Retaining the FQPA Safety Factor

The Committee concluded that the **10x** FQPA Safety Factor should be retained. Previously (November 20, 1998), the Committee recommended a 3x FQPA Safety Factor due to the lack of a DNT. At the current meeting, however, the Committee recommended that the 10x FQPA Safety Factor should be retained because there was not reliable data available to address the following concerns or uncertainties raised by the following matters: 1) evidence for increased susceptibility of young rats, 2) additional evidence for endocrine disruption, 3) uncertainty regarding the neuroendocrine effects in the young, and 4) the need for a DNT.

3. Population Subgroups for Application of the Safety Factor

The Committee determined that the FQPA safety factor (10x) is applicable for all populations when assessing acute and chronic dietary exposure. There are no longer any residential uses for this chemical, so the FQPA Safety factor does not apply to the short-term or intermediate-term exposure scenarios.